CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208351Orig1s000

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
Division Antiviral Products
10903 New Hampshire Ave
Silver Spring, Md. 20993
February 2, 2016

From: William B. Tauber, M. D.
Medical Officer DAVP

To: NDA 208351

Subject: Financial Disclosure Regarding: GS-US-366-1159, GS-US-366-1651 and GS-US-366-1689

PURPOSE AND SCOPE OF MEMO

This memorandum is intended to document statements made by Gilead Sciences Inc. regarding financial interests and possible conflicts of interest regarding Investigators who participated in the studies listed above. This Memorandum will be added to the Clinical Review of NDA 208351.

Financial Disclosure Statement: In Module 1.3.4 of the original submission dated 01 July 2015 under the Heading of List of Investigators who are Gilead Employees Gilead Sciences states: "None of the investigators who participated in covered Studies GS-US-366-1159, GS-US-366-1651, or GS-US-366-1689 is a full-time or part-time employee of Gilead. This statement is provided in accordance with 21 CFR 54.4." In addition, on Form OMB No. 0910-0396, Patricia Carlos, Manager of Regulatory Affairs for Gilead Sciences, Inc. certifies that no financial arrangement were established with listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, Patricia Carlos certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such interests. In a final statement, Patricia Carlos states: "I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)".

Discussion: In view of the statements made by the Applicant and the low likelihood of bias due to the objective nature of the data collected in these studies, I conclude no evidence of systematic bias due to financial interests of the investigators was discovered in the studies listed above.

Recommendations: Accept the data from these studies as unbiased.

Date February 3, 2016
William B. Tauber, M.D.
CDER/OAP/DAVP

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/s/

WILLIAM B TAUBER
02/03/2016

RUSSELL D FLEISCHER
02/03/2016

Clinical Review

Date	December 1, 2015
From	William Tauber, M.D. Medical Officer
Subject	Clinical Review
NDA/Supplement	NDA 208351
Applicant	Gilead Sciences
Date of Submission	July 1, 2015
PDUFA Goal Date	March 1, 2016
Proprietary Name	Odefsey (Emtricitabine/Rilpivirine/Tenofovir alafenamide) FDC (FTC/RPV/TAF)
Dosage Form/Strengths	Single tablet containing 200mg/25mg/ (b) (4) mg of FTC/RPV/TAF
Proposed Indication(s)	A complete regimen for the treatment of HIV-1 infection in (b) (4) (b) (4) patients
Recommendation	Approval

1. Background

The Applicant is proposing approval of a fixed-dose combination (FDC) tablet containing emtricitabine, rilpivirine and tenofovir alafenamide. Emtricitabine, a nucleoside reverse transcriptase inhibitor (NRTI) and rilpivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) are individually indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Tenofovir alafenamide, a prodrug of the nucleotide reverse transcriptase inhibitor tenofovir (TFV), is approved as a component of the FDC Genvoya (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (10mg) approved November 5, 2015. The development program for the emtricitabine/rilpivirine/tenofovir alafenamide FDC is based upon the comprehensive development and approval of Genvoya which contains both emtricitabine and tenofovir alafenamide, Endurant (rilpivirine hydrochloride), and the pharmacokinetic (PK) bridging of the FDC to the three components of the approved agents. The bioavailability (BA)/bioequivalence (BE) trial GS-US-366-1159 is pivotal for and food effect Study GS-US-366-1651 is supportive of the approval of this application for emtricitabine/rilpivirine/tenofovir alafenamide 200mg/25mg/25mg as an FDC which is indicated as a complete regimen for the treatment of HIV-1 infection.

2. CMC

The selected dosage form of the emtricitabine/rilpivirine/tenofovir alafenamide (F/R/TAF) fixed-dose combination (FDC) tablets are an immediate-release dosage form containing 200mg of emtricitabine (FTC), 25mg of rilpivirine (RPV) and 25 mg of tenofovir alafenamide 25mg (TAF). F/R/TAF tablets are gray, capsule shaped, film

coated tablets debossed with “GSI” on one side and “225” on the other side. Please refer to the CMC review of Dr. Haripada Sarker for complete details.

3. Nonclinical Pharmacology/Toxicology
Extensive programs of nonclinical studies with emtricitabine, rilpivirine and tenofovir alafenamide have been previously conducted and reviewed. In view of the of the nonclinical safety profiles for each of these compounds, additional nonclinical combination safety studies with emtricitabine, rilpivirine and tenofovir alafenamide were not considered necessary to support this application. No new nonclinical pharmacology/toxicology data were submitted.

4. Clinical Pharmacology/Biopharmaceutics
Please refer to Dr. Mario Sampson’s Clinical Pharmacology Review for details.

Absorption, Food Effects, Bioavailability and Bioequivalence

BA/BE Studies Using the FDC (FTC/RPV/TAF):

The Applicant conducted BA/BE studies to support the FDC drug product.

Comparative BA and Bioequivalence Studies, Fed Conditions: Studies 366-1159 and 366-1651
The primary objectives of **Study 366-1159** was to evaluate the bioequivalence of the fixed drug combination tablet FTC/RPV/TAF at dosages of 200mg/25mg/25mg to Genvoya (E/C/F/TAF) at dosages of 150mg/150mg/200mg and 10mg for the FTC/TAF components and Edurant (rilpivirine 25mg) for the rilpivirine 25mg component of the FDC taken concurrently under fed conditions. The differences in tenofovir alafenamide dosage of 10 mg in Genvoya compared to 25mg in FTC/RPV/TAF is explained by the presence of cobicistat in Genvoya which as a (b) (4) has been demonstrated to achieve comparable TAF exposures when combined with TAF 10mg to those observed when TAF 25 mg is given alone.

Ninety-six healthy subjects were enrolled. Each received a single dose on days 1, 15 and 29 of one of the three study medications, the sequence of exposures determined by randomization. The results demonstrated that the emtricitabine, rilpivirine and tenofovir alafenamide exposures of the FDC FTC/RPV/TAF were bioequivalent to the FTC/TAF exposures of Genvoya and the RPV exposures of Edurant.

The primary objective of **Study 366-1651** was to assess the effect of moderate–fat food and the effect of high-calorie high-fat food on the PK of a single dose of FTC/RPV/TAF (200mg/25mg/25mg) FDC compared to administration in the fasted state. Sixty healthy subjects were enrolled. Each received a total of 2 doses of FTC/RPV/TAF FDC at days 1 and 11, one while fasting and one while fed one of the two options above. The sequence of exposures was determined by randomization. The results were as follows:

- Overall TAF exposure (AUC_{last}) increased by approximately 45% and 53% (moderate-fat and high-calorie fat conditions respectively when FTC/RPV/TAF FDC was administered under fed compared to fasted conditions. There was an hour delay in T_{max} with fed conditions.
- Overall FTC exposure (AUC_{inf}) decreased by approximately 9% and 12% (moderate-fat and high-calorie, high-fat conditions, respectively) when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed compared with fasted conditions and it was accompanied by a delay in median T_{max} from one hour to two hours.
- Overall RPV exposure (AUC_{inf}) increased by approximately 13% and 73% (moderate-fat and high-calorie, high-fat conditions, respectively) when the FTC/RPV/TAF FDC tablet (200/25/25 mg) was administered under fed compared with fasted conditions. It was accompanied by a delay in median T_{max} of one hour with moderate fat but no delay with high fat compared to fasting.

Reviewer comment: Similar increases in TAF exposures with food were demonstrated in the Genvoya NDA. The FTC decreases and RPV increases were assessed by the Applicant as being clinically unimportant. The FDA concurs with the Applicant on this issue. .

DDI Studies Using the FDC (FTC/RPV/TAF):

Drug-Drug Interaction Potential FTC/RPV/TAF and Ledipasvir/Sofosbuvir (LDV/SOF) Fed Conditions: Study 366-1689.

The primary objectives of **Study 366-1689** were: 1. to evaluate the steady-state pharmacokinetics (PK) of FTC, RPV and TAF upon administration of FTC/RPV/TAF FDC with LDV/SOF FDC; 2. To evaluate the steady state PK of SOF its metabolites GS-566500 and GS-311007 and LDV upon administration of LDV/SOF FDC with FTC/RPV/TAF FDC. Forty-two healthy subjects were enrolled. Subjects were randomized 1:1:1:1:1:1 to 1 of 6 treatments sequences and received the following three treatments for 11 days each:

- **LDV/SOF:** LDV/SOF (1 × 90/400 mg tablet once daily) administered orally under fed conditions in the morning (Treatment A)
- **FTC/RPV/TAF:** FTC/RPV/TAF (1 × 200/25/25 mg tablet once daily) administered orally under fed conditions in the morning (Treatment B)
- **LDV/SOF+ FTC/RPV/TAF:** LDV/SOF (1 × 90/400 mg tablet once daily) plus FTC/RPV/TAF (1 × 200/25/25 mg tablet once daily) coadministered under fed conditions in the morning (Treatment C)

The results demonstrated that the co-administration of LDV/SOF with FTC/RPV/TAF did not notably affect the PK of FTC, RPV, or TAF. Compared to administration of FTC/RPV/TAF alone, LDV/SOF+FTC/RPV/TAF led to increases in TFV exposure (AUC_{tau}) of 75%, TFV C_{max} of 62%, and C_{tau} of 85%. In the Applicant's assessment,

these differences are not considered clinically relevant and no dose adjustment of FTC/RPV/TAF is necessary when coadministered with LDV/SOF. The FDA concurs with the Applicant in this assessment.

Coadministration of FTC/RPV/TAF with LDV/SOF did not notably affect the PK of LDV or SOF (including its metabolites GS-566500 or GS-331007).

5. Clinical Microbiology
No clinical microbiology data was submitted for these BA/BE studies which enrolled healthy HIV-1 uninfected subjects. For more information regarding the microbiology data relevant to FTC/TAF please see Dr. Lisa Naeger's reviews in NDA 207561 and NDA 202022 for rilpivirine.

6. Clinical/Statistical-Efficacy
No efficacy trials using the FDC drug product, FTC/RPV/TAF were submitted in this application. Efficacy assessment of the FDC is based upon demonstration of bioequivalence of the drug exposure. Please refer to NDA 207561 for details regarding the efficacy of the FTC/TAF components and NDA 202022 for details regarding the efficacy of the rilpivirine component.

7. Safety
Emtricitabine and rilpivirine at the dosages found in the FDC submitted for approval have been marketed for several years. The safety profiles of these two drugs when used in combination with other antiretrovirals (ARVs) are well known. TAF is a new ARV approved on November 5, 2015 as a component of the FDC Genvoya (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide). Tenofovir alafenamide is a prodrug of tenofovir similar to tenofovir disoproxil fumarate (TDF) whose safety profile is well established. Extensive safety data from clinical trials in which tenofovir alafenamide was administered were considered during the approval of Genvoya.

The 156 subjects in the BA/BE studies were administered three doses of study drugs (366-1159) or two doses of study drugs (366-1651) at 14 day and 11 day intervals respectively. The study drugs for 366-1159 were FTC/RPV/TAF 25 mg, RPV 25mg or EVG/COBI/FTC/TAF 10mg. The study drug in 366-1651 was FTC/RPV/TAF 25mg and the variable tested was food intake comparing fasted with moderate fat and high fat meal at time of administration.

BA/BE Studies Using the FDC (FTC/RPV/TAF):
Adverse Events:

Twenty-one out of 96 subjects (22%) in **Study 366-1159** experienced a total of 31 Grade 1 adverse events. As noted in Table 1, most adverse events occurred in few subjects with the possible exception of constipation in the rilpivirine only arm 7/96 vs 2/96 in the other two treatment arms. There were 4 instances of nausea/vomiting or gi

disturbances with E/C/F/TAF compared to 2 and 1 in the other arms. Patients were confined during this portion of the trial and the constipation may be dietary in origin. There were two discontinuations not due to adverse events. There were no serious adverse events and no deaths.

Thirteen of 60 subjects (22%) in **Study 366-1651** experienced a total of 14 Grade 1 adverse events. Upper respiratory inflammatory symptoms were noted in 5 fasting subjects compared to only one in the high fat meal subjects and none in the moderate fat meal subjects. The remainders of adverse events were single events. The cause of the increased numbers of upper respiratory symptoms including sore throat and nasal congestion among the fasted recipients is not known. As previously discussed, subjects were confined in close proximity. The apparent clustering may be the result of viral contagion. There is no obvious scientific explanation why administration of the study drug while fasted would increase vulnerability to viral infections. There were no serious adverse events, no discontinuations and no deaths in this study.

Table 1 Summary Adverse Events Studies 1159 and 1651

	1159 N=96 All Subjects participated in all three treatments All Adverse Events were Grade 1			1651 N=60 All Subjects were administered Study Drug while fasting and 30 each moderate or high fat alternative All Adverse Events were Grade 1		
	A= F/RPV/TAF (25)	B= RPV alone	C= E/C/F/TAF (10)	A=F/R/TAF (25) fasting	B= F/R/TAF (25) mod fat	A=F/R/TAF (25) high fat
TOTAL	8/96 (8%)	14/96 (15%)	9/96 (9%)	9/60 (15%)	1/30 (3%)	4/30 (13%)
Musculoskeletal	0	0	0	0	0	1
Headache/neuro	3	1	2	1	0	0
URI Sx	1	0	0	5	0	1
Derm	0	2	0	1	0	0
Constipation	2	7	2	1	1	0
Nausea/Vomiting GI symptoms	1	2	4	0	0	1
Dizziness	0	0	0	0	0	0
Fever	1	1	0	0	0	0
Infection	0	0	1	0	0	0
Dental	0	1	0	1	0	0
Dysmenorrhea	0	0	0	0	0	1

Laboratory Abnormalities

Fifty-five graded laboratory abnormalities were noted in **Study 366-1159** (Table 2). One subject with asymptomatic Grade 3 serum amylase and Grade 4 lipase and 8 episodes of Grade 3 hematuria all occurring in women, (5 at the time of menses) were observed. Otherwise laboratory abnormalities were mostly grade 1 or 2 and were balanced across the three treatment arms. There were numerically more instances of grade 1 serum

glucose increases in the FTC and TAF containing arms compared to the rilpivirine alone arm. Not all of these glucose determinations were conducted under fasted conditions.

Twenty-one graded laboratory abnormalities were noted in **Study 366-1651** (Table 2). All laboratory abnormalities except for grades two and three hematuria in women were grade 1. Mild elevations in serum hepatic transaminases were noted in three subjects.

Table 2 Summary Laboratory Abnormalities Studies 1159 and 1651

	1159 N=96 All Subjects participated in all three treatments			1651 N=60 All Subjects were administered Study Drug while fasting and 30 each were given moderate or high fat		
	A= F/RPV/TAF	B= RPV alone	C= E/C/F/TAF	A=F/R/TAF fasting	B= F/R/TAF mod fat	A=F/R/TAF high fat
Totals	18/96 (19%)	16/96 (17%)	21/96 (22%)	13/60 (22%)	3/30 (10%)	5/30 (17%)
Serum Glucose	4 (all G1)	2 (all G1)	6 (5G1.1G2)	0	0	0
Amylase Increase	2 (all G1)	2 (1G1,1G3)	1 (all G1)	0	0	1 (all G1)
Lipase Increase	0	1 (G4)	0	0	0	0
Hypophosphate	1 (all G1)	1 (all G1)	1 (all G1)	0	0	0
GGT.ALT, AST elevated	0	0	0	2 (all G1)	0	1(all G1)
Uric Acid Elevated	1 (all G1)	3 (1G2)	0	0	0	0
Neutrophils Low	1 (all G1)	1	1 (all G1)	0	0	1 (all G1)
Hemoglobin Low	2 (all G1)	0	0	3 (all G1)	0	0
Platelets Low	0	0	1 (all G1)	0	0	0
Urine Protein	3 (all G1)	2 (all G1)	6 (5G1,1G2)	1(all G1)	0	0
Urine Blood	4(1G1, 3G3)	4 (2G1,1G2,1G3)	5 (1G2,4G3)	7(4G1,1G2,2G3)	3 (1G1.1G2,1G3)	2 (all G1)

DDI Studies Using the FDC (FTC/RPV/TAF):
Adverse Events

In Drug-Drug Interaction **Study 366-1689** 42 healthy individuals were administered LDV/SOF FDC, FTC/RPV/TAF 25 mg FDC or LDV/SOF + FTC/RPV/TAF 25mg once daily for 11 days each. The numbers of subjects reporting AEs were similar between the three study arms but the numbers of adverse events were increased in the FTC/RPV/TAF arms compared to LDV/SOF arm alone (Table 3). The most prevalent AE for LDV/SOF was nausea, the most prevalent AE for FTC/RPV/TAF alone was

constipation and constipation, nausea/vomiting and headache in the FTC/RPV/TAF + LDV/SOF arm. The two instances of nausea and vomiting with LDV/SOF were the only investigator related AEs. All AEs were either Grade 1 or 2. There was a single discontinuation for the adverse event of colitis in the combined FTC/RPV/TAF + LDV/SOF arm. There were no other discontinuations for adverse events, no serious adverse events and no deaths during the conduct of this trial.

Table 3 Summary Adverse Events Study 1689

	1689 Except as noted, all AEs were Grade 1 (mild)		
	LDV/SOF	F/RPV/TAF	LDV/SOF + F/RPV/TAF
Totals AEs	7/42 (17%)	9/42 (21%)	11/42 (26%)
Total Subjects	7 (17%)	6 (14%)	8 (19%)
Musculoskeletal	2	0	0
Headache/neuro	0	2	2
URI Sx	1	1	1
Derm	0	1 (1G2)	1
Constipation	1	4 (1G2)	2
Nausea/Vomiting GI symptoms	2	0	4 (1G2)
Dizziness	1	0	0
Fever	0	0	0
Infection	0	1 (1G2)	1 (1G2)

Laboratory Abnormalities

Approximately 50% of subjects in all three treatment arms were found to have post administration laboratory abnormalities. The majority of these laboratory abnormalities were grade 1 or 2. The most common laboratory abnormality was elevated total cholesterol followed by LDL cholesterol. Cholesterol and LDL-cholesterol elevations have been identified with use of TAF. In contrast to the experience with the bioequivalence studies, elevated serum glucoses were not detected in this study. Urine protein and detection of urinary blood occurred mostly in women associated with their menses.

Table 4 Summary Laboratory Abnormalities Study 1689

	1689		
	LDV/SOF	F/RPV/TAF	LDV/SOF + F/RPV/TAF
Total Subjects with Graded Lab Abnorm	17 (41%)	20 (48%)	20 (48%)
Cholesterol	6 (2 G2)	7 (1 G2)	7 (1 G2)
LDL-CHOL	5 (1G2,1G3)	8 (2G2,1G3)	7 (1G2,1G3)
Serum Glucose High	0	0	0
Amylase Increase	0	1 (all G1)	0
GGT.ALT, AST	0	3(2 G1, 1G3)	2 (all G1)

elevated			
Uric Acid Elevated	3 (all G1)	2(all G1)	1 (all G1)
Neutrophils Low	1 (G1)	1 (all G1)	1b(all G1)
Hemoglobin Low	1 (all G1)	0	1 (G2)
Platelets Low	0	1 (all G1)	0
Urine Protein	3 (all G1)	0	2 (all G1)
Urine Blood	1 (all G1)	3 (2 G2,1 G3)	1 (G2)

Safety Summary:
Limited safety data from the BA/BE studies and the Drug-Drug Interaction study did not generate any new safety concerns for the FTC/RPV/TAF FDC.

The data from all three studies indicate a possible association between constipation and rilpivirine usage including an individual with grade 2 constipation. This potential link to rilpivirine must be tempered by the knowledge that study subjects were physically confined to the study center for the duration of the study. Their diet and activity at the center may have differed from that of their home environment. There was a single discontinuation for the adverse event of colitis in the combined FTC/RPV/TAF + LDV/SOF arm.

As might be anticipated from the multiple day administration, the percentage of adverse events and abnormal laboratory results were higher in Study 366-1689 compared to the two bioequivalence studies. Total cholesterol and LDL-cholesterol increases were only noted in the multiple daily dosing regimens and were higher when the subjects were receiving a regimen containing TAF.

8. Advisory Committee Meeting

Not applicable

9. Pediatrics

This NDA does not contain pediatric data. Pediatric trials with rilpivirine and tenofovir alafenamide are ongoing. An Agreed Initial Pediatric Study Request (iPSP) has been submitted to the Agency and after discussion was agreed upon. A partial waiver from conducting pediatric studies with FTC/RPV/TAF in pediatric subjects < 6 years of age weighing less than 25 mg was granted. A deferral request of the study of pediatric subjects > 6years and < 12 years was submitted as a iPSP. The study of this age group of pediatric patients is ongoing at this time.

10. Other Relevant Regulatory Issues

No additional regulatory issues have been identified.

11. Labeling

Review and discussions with the Applicant regarding of the contents of this product label are ongoing at the time of this clinical review.

12. Outstanding Issues

There are no items that need to be resolved prior to approval of this NDA.

13. Recommendations/Risk Benefit Assessment

I recommend approval of Emtricitabine/Rilpivirine/Tenofovir alafenamide 200mg/25mg/25mg (FTC/RPV/TAF), a fixed-dose combination (FDC) of two nucleoside-nucleotide reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor, as a complete regimen for the treatment of HIV-1 infection in (b) (4) (b) (4) who are fully suppressed on another Antiretroviral Regimen (ARV) for 6 months and are without history of virologic failure on ARV but who desire or require for non-virologic reasons a switch of ARV. Other stipulations of the indicated population would include: age 12 years or older ((b) (4) (b) (4) baseline estimated creatinine clearance by Cockcroft-Gault equation calculation of 30mL/min or higher and a baseline HIV-1 RNA less than or equal to 100,000 copies/mL. This recommendation is based on the bioequivalence of the individual component exposures of FTC/RPV/TAF to exposures of the approved rilpivirine dosage and FTC and TAF in the approved FDC E/C/F/TAF. The safety data reviewed were limited but did not identify any new safety signals indicating a modification of the risk benefit ratio of the component parts when combined was needed.

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/s/

WILLIAM B TAUBER
12/01/2015

RUSSELL D FLEISCHER
12/01/2015